Bladder Cancer, Drinking Water Source, and Tap Water Consumption: A Case-Control Study[1,2]

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ABSTRACT—Data from a population-based case-control interview study of incident bladder cancer in 10 areas of the United States were used to estimate relative risks among white men (2,116 cases, 3,892 controls) and women (689 cases, 1,366 controls) according to beverage intake level and type of water source. Individual year-by-year profiles of water source and treatment were developed by linking lifetime residential information with historical water utility data from an ancillary survey. Risk of bladder cancer increased with intake level of beverages made with tap water. The odds ratio (OR) for the highest vs. lowest quintile of tap water consumption was 1.43 [95% confidence interval (CI)=1.23, 1.67; χ^2 for trend=26.3, $P<.001$]. The risk gradient with intake was restricted to persons with at least a 40-year exposure to chlorinated surface water and was not found among long-term users of nonchlorinated ground water. The ORs for the highest vs. lowest quintiles of tap water intake were 1.7 and 2.0, respectively, among subjects with 40-59 and ≥60 years' exposure. Duration of exposure to chlorinated surface water was associated with bladder cancer risk among women and nonsmokers of both sexes. Among nonsmoking respondents with tap water consumption above the population median, the OR increased with exposure duration to a level of 3.1 (CI=1.3, 7.3; χ^2 for trend=6.3, P=.01) for ≥60 years of residence at places served by chlorinated surface water (vs. nonchlorinated ground water users). These results extend findings of earlier epidemiologic studies and are consistent with environmental chemistry and toxicologic data demonstrating the presence of genotoxic by-products of chlorine disinfection in treated surface waters.—JNCI 1987; 79:1269-1279.

Halogenated organic compounds are inadvertent by-products of water chlorination (*1-5*). Treated surface waters usually have much higher levels than treated or nontreated ground waters, due to elevated levels of precursor organics and heavier chlorination (*6, 7*). Epidemiologic evidence, primarily from ecologic surveys and case-control studies based on death certificates, supports the hypothesis that some chlorination by-products are carcinogens and suggests bladder, colon, and rectal cancers for further study (*8-25*). Specific hypotheses are that higher risks are conferred by long-term ingestion of chlorinated surface water vs. nonchlorinated ground water and that risk is associated with ingestion level. The biologic rationale for an effect is provided by a panoply of toxicologic studies (*26-41*).

A large population-based case-control interview study of bladder cancer conducted in 1978 by the National Cancer Institute and collaborators (*42, 43*) provided an opportunity to evaluate risk associated with drinking water source and treatment in more detail and within a larger study population than previously possible. By linking personal residential histories with information from water utilities, we assembled a lifetime water source-treatment profile for each study subject and used these data in epidemiologic evaluations

METHODS

Epidemiologic study.—We identified and interviewed 2,982 subjects (cases) and 5,782 controls in a collaborative population-based case-control study in 10 geographic areas of the United States. Eligible cases com-

ABBREVIATIONS USED: CI=95% confidence interval; OR=odds ratio; p-y=person-years; SMSA=standard metropolitan statistical area; THM=trihalomethane.

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prised all persons, 21-84 years of age, newly diagnosed with histologically confirmed cancer of the urinary bladder in a 1-year period beginning in December 1977. Cases were identified by tumor registries in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program and the New Jersey Cancer Registry. Geographic areas included Metropolitan Atlanta, Detroit, New Orleans, San Francisco, and Seattle and the States of Connecticut, Iowa, New Jersey, New Mexico, and Utah.

Controls were randomly selected from the general population, frequency matched to cases by sex, 5-year age group, and geographic area, with a 2:1 matching ratio in most places. In Detroit, the matching ratio was 1:1 and in New Jersey, 1.5:1. Controls 21-64 years of age were selected by telephone sampling by use of random-digit dialing (*44*), and controls 65-84 years of age were selected from a random 1% sample listing from the Health Care Financing Administration roster, estimated to cover 98% of the U.S. population older than 64 years of age (*43*). A more complete description of study design and methods is presented elsewhere (*43*).

Trained interviewers administered a standardized questionnaire to subjects in their homes. Questionnaire items included demographic background, lifetime use of artificial sweeteners and tobacco products, coffee consumption, use of hair dyes, a lifetime occupational history, and a history of relevant medical conditions. Levels of ingested tap water and other beverages were obtained by asking the level of consumption in a typical week, by beverage, in the winter a year prior to interview. A lifetime residential history with water source at each place was also gathered. Subjects provided the name of each city and town of residence for at least 1 year, with the starting and ending year at each place, and described the primary drinking water source as a private well, the community supply, bottled water, or another (specified) source. If the type of water source had changed during residence at one place, and type and year of the change was provided. Places of residence were coded with a standard geocoding system (*45*).

Survey of water utilities.—Water utilities serving more than 1,000 persons in the 10 study areas were surveyed in a separate data collection. Using a standardized form, trained data collectors interviewed utility personnel and abstracted records at a site visit to each community supply. The survey covered 1,102 water utilities in the study areas and also included Chicago and New York City because many respondents had lived in these places. Data collectors recorded all water sources, treatments, and the places where water was distributed since 1900. Water sources were classified as surface or ground. Potential sources of contamination were recorded for surface water sources with unprotected watersheds. Ground waters were classified as originating from springs or wells. For wells, the depth, aquifer, and recharge characteristics were noted. Disinfection and other chemical and mechanical treatments were also recorded. We found that data were commonly available describing the years during which chlorine disinfection had been used, but information on amounts of added chlorine was often lacking. Towns and cities served by each water source, with the time period served, were geocoded with the same system as that for residential histories, to facilitate their linkage. This information on water source (surface and/or ground) and chlorination status (chlorinated or not chlorinated) was used to develop a personal exposure profile for each respondent.

At the site visit, data collectors also gathered a water sample from each community supply for chemical analysis. Analyses measured halogenated organic volatiles, including THMs. Methods and results for sample collection and analysis are presented elsewhere (*46*).

Epidemiologic analyses.—Information from the residential history of each study subject was merged with data from water utilities to create an exposure history with a year-by-year description of water source and treatment. This profile was used to develop indices of lifetime exposure to drinking water from different types of sources and water treatment. Total beverage consumption was divided into two major components, beverages derived from tap water [coffee, tea (hot and iced)], ¾ of reconstituted frozen juice, tap water per se, and beverages from other sources (other fruit juices, beer, wine, liquor, milk, soft drinks). The amounts of water in beverages usually made with boiled tap water [coffee and tea (hot and iced)] or nonheated water (water per se, reconstituted juices) were summed separately, since boiling tap water can decrease levels of dissolved chlorine and volatile organics.

The OR was used to estimate the relative risk. Logistic regression for unmatched data was used to obtain the unconditional maximum likelihood point and CI estimates of the OR and to adjust for potential confounding effects of selected variables (*47*). Potential confounders in most logistic regression models were: sex, age (<45, 45-64, ≥65 yr), study area (10 strata), cigarette use [six levels: never smoked, former smoker (<20, ≥20 cigarettes/day), and current smoker (<20, 20-39, ≥40/day)], ever employed in a high-risk occupation (yes or no; high-risk occupation was one in this study population with a relative risk of 1.5+), and the population size or urbanicity of the place of longest lifetime residence [three levels: <50,000 and not in an SMSA, <50,000 and within an SMSA, and ≥50,000 (in an SMSA)]. Confounding variables were evaluated by examining their covariation with water exposure variables in the control series and by OR calculations in models with and without the confounders. Analyses were restricted to white respondents, numbering 2,805 cases and 5,258 controls. Among these, information on cigarette smoking history was incomplete for 65 cases and 107 controls who were thus excluded from most analyses.

RESULTS

Drinking Water Source and Tap Water Consumption

Cases and controls were similar in their overall proportions of numbers of years of residence with each type of water source (table 1). Between 1900 and 1978, the interview year, cases experienced a total of 188,708 p-y and controls, 352,705 p-y. Cases reported 40,189 p-y (21.3%) at residences with nonchlorinated well or spring water, both private and community, and controls, 82,604 p-y (23.4%). Community water sources of all types accounted for 75.5% of case p-y and for 73.7% of control p-y. The overall proportion of case p-y and control p-y at residences served by chlorinated surface sources was similar (32.6 and 30.4%). Of all respondent-years lived at residences served by community supplies, we had surveyed historical water utility information for 109,272 case p-y (76.7%) and 197,959 (76.2%) control p-y. Water source information was not available for periods when respondents used a community supply in places of less than 1,000 population or in places outside of the study areas, because these places were not covered by our water utility survey.

Average duration of residences with different types of water source and levels of tap water consumption are shown in table 2 for all white controls and for subgroups characterized by other potential risk factors. There was little difference in mean duration by sex, by employment (ever) in a high-risk occupation for bladder cancer, or by lifetime number of lower urinary tract infections. The mean duration at residences with either type of water sources increased with age, as expected. The reporting center was the most important determinant of the type of water source used. The mean duration of nonchlorinated ground water use varied from 7.4 years among San Francisco respondents to 39.5 years among Iowa control subjects. Duration of chlorinated surface water use (not mixed with other waters) varied from 1.6 years in Utah to 42.4 years in Detroit. Seattle is predominantly served by chlorinated surface water, but parts of the city use ground water; so the duration of unambiguous chlorinated surface water use was low (4.7 yr). Duration of groundwater use was inversely associated with intensity of cigarette smoking, whereas duration of surface water use showed a small positive association with cigarette use. Duration of chlorinated surface water use was elevated for respondents whose longest lifetime residence was in urban areas, whereas duration of groundwater use was higher among small town or rural dwellers.

Average daily tap water intake from all beverages among control subjects is also shown in table 2. Patterns of total beverage fluid consumption (not shown) were similar to the pattern shown for tap water alone. Men consumed 2.01 liters/day total fluid, of which 1.40 liters (70%) was derived from tap water. Women consumed 1.72 liters/day, with 1.35 liters (79%) from tap water. Total beverage and tap water consumption varied more with cigarette smoking level than with other characteristics. Current smokers of ≥40 cigarettes/day consumed 1.64 liters (64% of total fluid) tap water, whereas nonsmokers drank 1.28 liters (74% of total fluid) of tap water.

Fluid and tap water intake decreased with increasing population size of the place of longest residence. There was some variation among study areas, with controls from Iowa and New Orleans reporting the highest levels and those from New Jersey, Detroit, Utah, and San Francisco the lowest. The low tap water consumption reported from Utah reflected low coffee consumption. Intake varied slightly, in the expected positive direction, with number of lower urinary tract infections.

Risk by Total Beverage and Tap Water Consumption

Among the white subjects, there was complete information on beverage consumption and cigarette smoking habit for 2,035 male cases, 3,758 male controls, 660 female cases, and 1,323 female controls. Effects on risk of total beverage and tap water consumption were evaluated using two logistic regression models. The first multivariate regression model included a term for daily total beverage fluid in liters as a continuous variable, and the second model included terms for the daily tap water and nontap beverage components as separate continuous variables. Both models also included terms for potential confounders, including smoking, occupation, geographic area, age, and sex. Regression coefficients from these calculations represent the logarithm of the OR (in units liter). In sex-specific models, the regression coefficient for total beverage fluid consumption was 0.112 for men, 0.117 for women, and 0.122 overall ($P<.0001$). Separation of total fluid consumption into its tap and nontap water components indicated that risk was primarily associated with the tap water component. Among men the coefficients for tap and nontap beverages were 0.176 ($P<.0001$) and 0.037 ($P=.42$) and among women, 0.123 ($P=.09$) and 0.089 ($P=.39$), respectively.

Chlorinated surface waters contain both volatile and nonvolatile chlorination by-products. Volatiles are partially removed through boiling. When tap water was further separated into variables for its heated (coffee and

TABLE 1.—*P-y of experience among white respondents at residences served by various types of water source, by case-control status*

Type of water source	Cases, n=2,805		Controls, n=5,258	
	P-y	Percent	P-y	Percent
Private (not chlorinated)				
Well or spring	34,198	18.1	70,809	20.1
Municipal (not chlorinated)				
Well or spring	5,991	3.2	11,795	3.3
Surface or mixed surface and ground	4,632	2.5	8,636	2.5
Municipal (chlorinated)				
Single sources				
Well or spring	13,950	7.4	24,657	7.0
Surface	61,542	32.6	107,328	30.4
Mixed surface and ground	23,157	12.3	45,543	12.9
Municipal (source and chlorination status unknown)	33,216	17.6	61,879	17.5
Other, unknown	12,022	6.4	22,058	6.3
Total	188,708		352,705	

TABLE 2.—*Duration at a residence with selected drinking water sources and tap water consumption levels among white controls, by characteristics of study subgroup*

Characteristic	No.	Duration, yr		Tapwater consumption, liter/day
		Ground, not chlorinated water	Surface chlorinated water	
Total group	5,258	15.7	20.4	1.39
Sex				
Males	3,892	16.1	20.0	1.40
Females	1,366	14.5	21.6	1.35
Age, yr				
21-44	291	6.6	12.0	1.30
45-64	1,991	11.9	18.9	1.48
65-84	2,976	19.2	22.2	1.33
Reporting center				
Atlanta	207	13.2	23.4	1.39
Connecticut	844	14.0	27.9	1.37
Detroit	429	11.1	42.4	1.33
Iowa	743	39.5	4.5	1.61
New Jersey	1,542	10.5	20.0	1.27
New Mexico	165	25.4	3.4	1.49
New Orleans	112	9.9	40.3	1.61
Seattle	316	11.2	4.7	1.44
San Francisco	621	7.4	31.5	1.36
Utah	279	15.4	1.6	1.35
Cigarettes				
Never	1,987	17.3	19.8	1.28
Former smoker				
<20/day	645	17.6	20.0	1.35
≥20/day	1,230	15.7	20.4	1.45
Current smoker				
<20/day	413	14.3	19.3	1.42
20-39/day	705	11.8	21.9	1.54
≥40/day	171	10.3	22.4	1.64
High-risk occupation (ever?)				
No	4,550	15.6	20.4	1.37
Yes	708	16.1	20.7	1.45
Lower urinary tract infection (lifetime)?				
Never	4,201	15.7	20.9	1.37
1-2	656	15.0	20.0	1.40
≥3	339	17.0	16.8	1.54
Population size, usual lifetime residence				
<50,000, not in SMSA	994	35.4	5.5	1.48
<50,000, in SMSA	1,557	15.5	17.6	1.39
≥50,000, in SMSA	2,444	7.7	29.4	1.36

tea) and nonheated (water per se and reconstituted juices) fractions, both were significantly associated with bladder cancer risk among male respondents, with the coefficient for the heated portion (made up of coffee and tea) of higher magnitude. The regression coefficients from the regression among men were 0.227 ($\chi^2=15.3$) and 0.139 ($\chi^2=8.14$) for heated and nonheated tap water, respectively. Among women, the contribution of nonheated tap water was the larger (and statistically significant). Regression coefficients were 0.035 ($\chi^2=0.10$) and 0.177 ($\chi^2=3.88$) for heated and nonheated tap water, respectively. From the model that included both sexes (and adjusted for sex), the respective coefficients were 0.190 ($\chi^2=13.9$) and 0.156 ($\chi^2=13.3$). These results were consistent with an effect of nonvolatile contaminants from tap water present in both heated and nonheated beverages. In this same model, the coefficient (per liter) for the association of the nontap water fraction of total fluid intake was 0.041 ($\chi^2=0.92$).

A possible explanation for the association of bladder cancer risk with water intake is that patients may have changed their drinking habits with development of disease. If so, consumption levels might be elevated among individuals with more advanced disease, with random variation within diagnostic category. Information on extent of disease was available for 1,645 white patients. We measured the association of risk with tap water intake within disease category by using all white controls in each analysis. Multivariate logistic regression models, similar to those reported above, were used to detect associations. Among the 452 patients with carcinoma in situ or confined to the mucosa, the regression coefficient was 0.099 ($\chi^2=2.2$). Among 465 patients with tumors extending into the submucosa or invading the musculature, the coefficient was 0.178 ($\chi^2=7.6$). Among 629 patients with disease limited to the bladder (all the above stages, not further defined), the coefficient was 0.144 ($\chi^2=6.8$); for cancer extending beyond the bladder (99 patients), the regression coefficient was 0.166 ($\chi^2=0.16$). These results provided no evidence that the overall association of bladder cancer risk with tap water intake resulted from differences in recent consumption related to extent of disease.

ORs by quintile of tap water consumption, relative to the lowest quintile (<0.81 liter/day) are shown in table 3. The relative risk increased with daily intake, with an OR of 1.47 among men and 1.29 among women for the highest vs. the lowest consumption quintile. The χ^2 for trend was highly significant for both sexes combined and among men ($P<.0001$) but not among women. These results were consistent with findings from the logistic regression models with use of continuous variables.

Risk by Tap Water Intake and Duration of Chlorinated Surface Water Use

Evaluation of bladder cancer risk by the combined effects of duration of chlorinated surface source use and tap water intake required that analyses be restricted to individuals with reliable information for both items. The small number of respondents with incomplete tap water intake records were eliminated from the analysis. The question of whom to remove among respondents with partially complete water supply information was more difficult to address. Many respondents reported some use of community water in places that were not in the water utility survey, because they had lived in places outside of study areas or some of their residences were in places with populations of less than 1,000. Water source for these subjects was incompletely characterized. In addition, some of the surveyed water utilities used both surface and subsurface waters that were mixed at the water plant or directly delivered to different parts of their service districts. In such cases the relative proportion of water from different sources was variable and not available on a yearly basis, and the proper exposure classification for people using such supplies could not be determined.

To minimize the influence of incomplete or ambiguous exposure information, subsequent analyses were restricted to cases and controls for whom the summed years at places served by chlorinated surface sources and nonchlorinated ground sources accounted for more than 50% of their lifetime. After eliminating the remaining subjects, the reduced study population included 1,225 male cases, 2,223 male controls, 405 female cases, and 804 female controls. The 4,657 cases and controls represented 57.8% of the total study population. The 3,027 controls eligible for inclusion were similar to excluded respondents with respect to sex, to cigarette smoking levels, to employment in high-risk occupations, and to number of lower urinary tract infections. Older subjects were more likely to be included than younger respondents, possibly due to more stable residential patterns and proportionally longer periods of residence in study areas. The proportion of subjects included in the reduced analysis group varied sharply by geographic area, due primarily to differences in the proportion of consumers served by utilities that used both surface and ground sources. Also, reporting centers with high in-migration rates had lower proportions of included respondents, because information was missing on municipal water utilities of migrants when they lived outside of study areas. Among the 10 study areas, the percentage of all white controls included in the reduced analysis were: Atlanta, 63%; Connecticut, 71%; Detroit, 87%; Iowa, 67%; New Jersey, 49%; New Mexico, 34%; New Orleans, 83%; Seattle, 12%; San Francisco, 70%; and Utah, 17%. Of the eligible group, persons with incomplete smoking histories (29 cases, 67 controls), incomplete tap water consumption information (9 cases, 21 controls), or both (1 case, 2 controls) were excluded from relative risk calculations.

Logistic regression analyses among the reduced study group estimated bladder cancer risk for fluid intake from all beverages, tap water, and nontap water as continuous variables, with the use of the same regression models as reported above for the complete study population. Results followed patterns found in the earlier analysis.

ORs for bladder cancer were calculated by duration of residence at places with chlorinated surface sources. The low-exposure comparison group were persons who had

TABLE 3.—*ORs for bladder cancer with level of daily tapwater ingestion, by sex*[a]

Tap water ingestion level, liter/day	Men			Women			Both sexes
	No. of cases	No. of controls	OR (CI)	No. of cases	No. of controls	OR (CI)	OR (CI)
≤0.80	326	782	1.00	120	265	1.0	1.0
0.81-1.12	366	775	1.12 (0.9, 1.4)	139	308	0.99 (0.7, 1.3)	1.08 (0.93, 1.26)
1.13-1.44	404	760	1.24 (1.0, 1.5)	116	279	0.90 (0.7, 1.2)	1.14 (0.98, 1.34)
1.45-1.95	441	729	1.39 (1.2, 1.7)	141	262	1.13 (0.8, 1.5)	1.32 (1.13, 1.54)
≥1.96	498	712	1.47 (1.2, 1.8)	144	209	1.29 (0.9, 1.8)	1.43 (1.23, 1.67)
χ^2, trend		22.6			3.15		26.5
P-value		<.0001			.08		<.0001

[a] From logistic regression, adjusted for: sex, age, high-risk occupation, smoking habit, population size of usual place of residence, and reporting center.

TABLE 4.—*ORs for bladder cancer with level of tapwater ingestion, by duration at a residence served by a chlorinated surface water source*[a]

Tap water ingestion level, liter/day	Year of residence with chlorinated surface water:														
	0			1-19			20-39			40-59			≥60		
	No. of cases	No. of controls	OR	No. of cases	No. of controls	OR	No. of cases	No. of controls	OR	No. of cases	No. of controls	OR	No. of cases	No. of controls	OR
≤0.80	43	108	1.0	32	60	1.0	71	133	1.0	95	238	1.0	26	53	1.0
0.81-1.12	55	133	1.0	33	63	1.0	80	186	0.8	126	206	1.6	23	58	0.8
1.13-1.44	54	129	1.2	39	62	1.2	69	152	0.8	107	198	1.3	28	51	1.1
1.45-1.95	49	156	0.8	35	64	0.9	94	142	1.2	125	174	1.7	28	33	1.7
≥1.96	67	126	1.2	49	78	1.0	110	145	1.2	122	159	1.7	31	30	2.0
χ^2, trend	0.12			0.02			3.49			7.51			6.09		
P-value	.73			.89			.06			.006			.014		

[a] From logistic regression, adjusted for: sex, age, high-risk occupation, smoking level, population size of usual residence, and reporting center.

never used surface water and whose customary source of water was a nonchlorinated spring or well. Among men and for both sexes combined, there was no increase in bladder cancer risk with increasing duration of surface water use. The OR for bladder cancer was 0.99 among men with ≥60 years' use of chlorinated surface water, relative to that among men with no use. However, bladder cancer risk among women increased with duration of surface water use, with a significant trend (χ^2=4.1, P=.04). Relative to women who never used chlorinated surface water, the OR was 1.5 for 1-19 years', 1.2 for 20-39 years', 1.5 for 40-59 years', and 2.1 (CI=1.1, 4.0) for ≥60 years' usages.

Table 4 shows OR for bladder cancer with increasing tap water intake level, within strata grouped by duration of residence at places with a chlorinated surface source. Risk did not increase with ingestion among those with no or 1-19 years' use reported for chlorinated surface water, Small, nonsignificant increases in risk with tap water consumption were found among persons with 20-39 years' exposure to chlorinated surface waters. Respondents with 40-59 or ≥60 years of surface water use showed the strongest bladder cancer risk gradients with tap water intake. The ORs were 1.7 and 2.0, respectively, for the highest vs. lowest consumption quintile. The test for trend with intake was significant within these two longest duration strata (P=.006 and .014).

When analyzed by geographic region, OR increased with total tap water intake in 8 of the 10 study areas, with a statistically significant positive trend in 3 places (New Jersey, Detroit, San Francisco). The trend was slightly negative (not significant) in 2 places (New Orleans and Iowa).

ORs for the combined effects of tap water ingestion level and duration of chlorinated surface water use are shown in table 5. Risks are relative to persons who consumed less than 0.81 liter daily and whose lifetime residences were at places served by nonchlorinated ground water and never by chlorinated surface sources (43 cases, 108 controls). Gradients of increasing risk with duration of chlorinated surface sources were observed only among those in the upper two quintiles of tap water consumption. Likewise, increasing ORs with level of tap water ingestion were present primarily among persons who lived at residences served by chlorinated surface water sources for at least 40 years. The OR for the 31 cases and 30 controls who reported the highest levels of water consumption (>1.91 liter/day) and who had resided in places served by chlorinated surface waters for at least 60 years was 1.8.

TABLE 5.—*ORs for bladder cancer with combined tap water ingestion level and duration of chlorinated surface water source*[a]

Ingestion level, liter/day	Year of residence with chlorinated surface water:				
	0	1-20	20-39	40-59	≥60
≤0.80	1.0 (43, 108)	1.2 (32, 60)	1.1 (71, 133)	0.8 (95, 238)	1.0 (26, 53)
0.81-1.12	1.1 (55, 133)	1.0 (33, 63)	0.9 (80, 186)	1.3 (126, 206)	0.8 (23, 58)
1.13-1.44	1.1 (54, 129)	1.4 (39, 62)	0.9 (69, 152)	1.1 (107, 198)	1.0 (28, 51)
1.45-1.95	0.7 (49, 156)	1.1 (35, 64)	1.3 (94, 142)	1.3 (125, 174)	1.7 (28, 33)
≥1.96	1.1 (67, 126)	1.1 (49, 78)	1.3 (110, 145)	1.4 (122, 159)	1.8 (31, 30)

[a] From logistic regression, adjusted for: sex, age, smoking habit, high-risk occupation, population size of usual place of residence, and reporting center. *Numbers in parentheses:* No. of cases, No. of controls.

Risk by duration of chlorinated surface water use is further explored in tables 6 and 7. These tables show OR for duration as stratified by sex and median population level of daily tap water consumption (+/− 1.4 l). Within the restricted study population (table 6), the risk gradient with duration was stronger for tap water ingestion above than for that below the median. Among women reporting elevated tap water intake, the χ^2 for trend with duration (of chlorinated surface water use) was significant (P=.02), with those exposed for ≥60 years having an OR of 3.2 (CI=1.2, 8.7), relative to that among the nonexposed. The gradient among men was much smaller, and the test for trend with duration not significant.

Evaluation of risk by smoking status revealed that most of the duration effect arose from nonsmokers (table 7). This partially explained the risk differences between the sexes observed in table 6, given the lower smoking rates among women. Among nonsmokers who consumed tap water in amounts above the median, the risk gradient was apparent in both sexes, with ORs of 3.6 among men and 3.7 among women in the longest duration category (≥60 yr). Among nonsmoking women, a significant increase in risk with duration of chlorinated surface water use was also observed for consumers with lower intake. Overall, ORs increased with duration of chlorinated surface water use among nonsmoking subjects who reported tap water consumption above the median (χ^2 trend=6.32, P=.01).

DISCUSSION

Bladder cancer risk in this study increased with total tap water consumption but not with intake of other beverages. This finding was similar in both sexes and generally consistent in the 10 study areas. Risk elevations with tap water consumption were largely restricted to subjects with at least 40 years' residence in places with chlorinated surface water sources. Bladder cancer risk was not linked with tap water consumption among respondents using nonchlorinated ground water for most of their lives. No overall pattern of elevated bladder cancer risk was seen with duration of chlorinated surface water use. However, when attention was restricted to study subjects reporting above-median levels of tap water ingestion, there were small increases in risk with the number of years exposed. Exposure duration (to chlorinated surface waters) and number of years since first exposure were highly correlated, preventing separate evaluation of exposure duration and time since first exposure. In analyses combining the effects of exposure duration (to chlorinated surface waters) and the level of tap water ingestion, greatest risk elevations were found among respondents with the highest levels of both. Among women, increases of risk with duration were much stronger than among men and were also apparent among those with lower levels of tap water ingestion. Associations of bladder cancer risk with exposure duration were apparently due mostly to effects among nonsmokers, and this partially explained the lack of concordance of the findings for men and women. Among men and women nonsmokers, the relative risk increased to 3.1 among those with ≥60 years of residence with a chlorinated surface water source.

Two other case-control studies of bladder cancer evaluated fluid consumption as a risk factor. Jensen et al. (*48*) in a study of 371 cases found significant increases in risk among men with increasing ingestion of coffee, tea, and soft drinks. The logistic regression coefficient for soft drink consumption among women

TABLE 6.—*ORs for bladder cancer with duration of residence with a chlorinated surface drinking water source, by sex and tap water ingestion level*[a]

Year	Men			Women			Both sexes
	No. of cases	No. of controls	OR (CI)	No. of cases	No. of controls	OR (CI)	OR (CI)
			Tap water consumption below median				
0	91	232	1.0	24	75	1.0	1.0
1-19	60	112	1.3 (0.8, 2.0)	21	42	1.4 (0.6, 3.0)	1.3 (0.9, 1.9)
20-39	149	120	1.2 (0.8, 1.8)	39	103	0.9 (0.4, 1.8)	1.1 (0.8, 1.6)
40-59	195	374	1.2 (0.7, 1.8)	70	171	1.1 (0.5, 2.3)	1.1 (0.8, 1.6)
≥60	35	89	0.8 (0.5, 1.5)	27	45	1.7 (0.7, 4.0)	1.1 (0.7, 1.7)
χ^2, trend		(−) 0.10			0.72		0.01
P-value		.75			.40		.91
			Tap water consumption above median				
0	124	267	1.0	29	78	1.0	1.0
1-19	81	131	1.1 (0.7, 1.6)	26	42	1.8 (0.8, 3.7)	1.2 (0.9, 1.7)
20-39	178	281	1.1 (0.7, 1.5)	58	98	1.5 (0.7, 3.1)	1.1 (0.8, 1.6)
40-59	234	328	1.2 (0.8, 1.7)	76	102	2.2 (1.0, 4.8)	1.3 (0.9, 1.9)
≥60	53	66	1.2 (0.7, 2.1)	21	25	3.2 (1.2, 8.7)	1.4 (0.9, 2.3)
χ^2, trend		0.59			5.40		2.80
P-value		.44			.02		.09

[a] From logistic regression, adjusted for: age, smoking habit, high-risk occupation, population size of usual residence, reporting center, and sex where appropriate.

TABLE 7.—*ORs among nonsmokers for bladder cancer with duration of residence with a chlorinated surface source, by sex and tap water ingestion level*[a]

Year	Men			Women			Both sexes
	No. of cases	No. of controls	OR (CI)	No. of cases	No. of controls	OR (CI)	OR (CI)
			Tap water consumption below median				
0	20	91	1.0	14	61	1.0	1.0
1-19	14	38	1.6 (0.7, 4.0)	9	33	1.2 (0.4, 3.7)	1.5 (0.8, 3.0)
20-39	25	87	1.0 (0.4, 2.6)	16	55	1.5 (0.5, 4.4)	1.2 (0.6, 2.4)
40-59	29	122	0.7 (0.3, 1.9)	41	117	2.1 (0.8, 5.9)	1.1 (0.5, 2.2)
≥60	10	25	1.3 (0.4, 4.4)	16	26	4.3 (1.3, 14.5)	2.0 (0.9, 4.6)
χ^2, trend		(−) 0.25			5.74		0.71
P-value		.62			.02		.40
			Tap water consumption above median				
0	17	83	1.0	18	56	1.0	1.0
1-19	5	31	0.8 (0.3, 2.5)	9	23	1.7 (0.5, 5.4)	1.1 (0.5, 2.4)
20-39	25	71	2.1 (0.9, 5.2)	19	46	1.8 (0.6, 5.4)	1.9 (1.0, 3.7)
40-59	35	96	2.5 (0.9, 6.6)	23	57	1.8 (0.6, 5.9)	2.0 (1.0, 4.1)
≥60	13	18	3.7 (1.1, 12.0)	14	18	3.6 (0.8, 15.1)	3.1 (1.3, 7.3)
χ^2, trend		5.45			2.00		6.32
P-value		.02			.16		.01

[a] From logistic regression, adjusted for: age, smoking habit, high-risk occupation, population size of usual residence, reporting center, and sex where appropriate.

was comparable to that for men, but numbers of subjects were small and the result was statistically unstable. A study from Germany of 431 patients and matched controls found elevated risks among men with levels of coffee, beer, spirits, and total beverage consumption (*49*). The relative risk was above 3.0, by use of different regression models, among daily consumers of 2 liters or more vs. men with lower intake. Results from both studies were adjusted for cigarette smoking level. Neither study evaluated the type of drinking water source. Our findings are somewhat discrepant with these. Almost all of the associations we found with total beverage intake could be attributed to its tap water component, whereas the two cited studies found significant associations with beer and soft drinks as well. Water used for beer production and soft drink production is customarily deionized and passed through activated carbon filters, removing most chlorination by-products, many other contaminants, and residual chlorine. In analyses not reported in detail herein, we attempted to see if the uneven elevations in risk among men associated with coffee intake in (*50*) could be ascribed to the tap water content, but we were unsuccessful in detecting independent effects.

Many past studies that investigated bladder cancer risk and drinking water source were ecologic in design (*8-16*). Most (*8-13*) but not all (*14-16*) reported positive association in one or more sex-race groups of adjusted bladder cancer morbidity or mortality rates with county or town use of a chlorinated surface water source, as contrasted with use of a nonchlorinated ground source. Five additional studies used a case-control approach based on death certificate records (*17-21*). Exposure was defined in these five studies as the water source serving the address listed on the death certificate. Two studies found significant associations of bladder cancer mortality with surface chlorinated (vs. ground nonchlorinated) source of water (*17, 18*). A study of limited statistical power from Washington County, Maryland, noted a twofold (nonsignificant) risk of incident bladder cancer among users of chlorinated surface water compared to deep well users (*22*). The size of OR estimates in the current study is consistent with these findings.

The current investigation avoided weaknesses of ecologic studies and death certificate-based case-control studies by gathering information directly from incident cases and frequency-matched comparison subjects (*43*). The lifetime residential history from each respondent and identification of the primary drinking water source at each residence (community or private source) permitted linkage with water utility data to define a year-by-year exposure history of water source and treatment type. Information on other important risk factors, including tobacco habit, occupational history, and population size of usual lifetime residence, allowed control for potential confounding and assessment of interaction. The large study population from multiple geographic locations increased the statistical stability of our findings, permitted geographic comparisons, and facilitated examination of risk among subgroups.

Limitations of this study are related to: the type and extent of interview information on beverage consumption, incomplete information on water source and treatment for very small communities and places outside of the 10 study areas, and few p-y of exposure at residences served by chlorinated ground water sources. Additionally, in assessing the implications of these findings, we were limited by the types of past contaminant information available for precise estimates of historical exposures.

To minimize the possible effects of seasonal variation on reported intake, we asked subjects about their beverage consumption "1 year ago, in the winter." Only minor variations in beverage intake by season of interview were found among controls, suggesting that posing the question in this way was successful in correcting for seasonal differences, if they existed. Another concern is how well lifetime consumption patterns are represented by reported levels of recent intake. A direct answer to this question was not available from information we gathered. The validity of retrospective dietary assessment has been reported from several studies, with most producing low to moderate correlations (0.3-0.7) with reference data from the past [(*51-55*); Block G: Personal communication]. Water consumption was not reported in these studies, but it is likely that validity patterns for water are similar to the food groups and nutrients that were measured. Random misclassification of exposure status is expected to dampen the strength of associations in this study. Daily tap water consumption levels observed here were consistent with those from a national dietary survey conducted by the U.S. Department of Agriculture in 1978 (*56*), increasing our confidence in the accuracy of the beverage consumption levels that subjects reported for their recent intake.

Since a primary motivation of this study was to evaluate saccharin as a human bladder carcinogen (*42*), study areas were not selected to optimize the detection of risk related to type of water source. For example, of the 10 geographic areas, 5 are metropolitan regions predominantly served by one water source. This fact limits intraregional variability of exposure in these places and reduces the statistical power of the study to detect differences. The exposure measures used in our analysis may overly simplify a complex exposure matrix by dichotomizing water sources into chlorinated surface and nonchlorinated ground. While based on extensive environmental and toxicologic information (*5, 6, 32-37, 57*), this classification ignores other potentially important differences among sources and may completely misclassify exposure in places with contaminated ground water.

Lacking specific information about water source and treatment for at least half of the lifetime of many respondents, we eliminated 41.9% of cases and 42.4% of controls from the study population for a series of "reduced" analyses in which the combined effects of source type-treatment and tap water ingestion level were evaluated. The subjects included in these analyses were similar to excluded subjects with regard to sex, cigarette smoking habit, employment in a high-risk occupation, number of lower urinary tract infections, and population size of the place of longest residence. The varying control-to-case ratios from the different areas were similar in the included and excluded groups. Therefore, there is little reason to suspect that bias was introduced when selecting this subpopulation. The gradient in bladder cancer risk with tap water intake among the excluded population was slightly greater than that among subjects included in the analyses. Older respondents were more likely to be included in the reduced analysis than younger subjects, and there was significant variation in inclusion rates among the study areas.

Our choice of exposure variable to represent type of water source and treatment was based on a large body of environmental chemistry information (*1-3, 5-7*) and is consistent with approaches taken in previous epidemiologic studies (*8-25*). Surface waters generally have much higher organic levels than ground waters and are usually more highly chlorinated. Organic contamination in surface waters can include man-made chemicals from industrial and municipal waste waters or runoff, as well as naturally occurring humic and fulvic acids. Chlorine reacts with organic compounds in the raw water to form THMs and a host of chlorinated nonvolatile compounds of higher molecular weight (*1, 2, 5*). Resulting levels of halogenated by-products in finished surface waters reflect these differences, while nonchlorinated ground waters are largely free of these contaminants (*6, 7*). Our measurements confirmed these observations (*46*). We used measurements of THM and chloroform from the utility survey to model levels of these chlorination by-products as a function of water source and treatment. In multivariate regression models, where the measured contaminant level was the dependent variable and indicator (1/0) variables represented water source characteristics, the surface/ground variable explained more than 50% of the variance in chlorination by-product level or its logarithmic transform (*46*). With this information as background, we sought to maximize the possibility of discovering elevated bladder cancer risk, if present, by measuring risk among users of chlorinated surface water, as contrasted to risk among subjects exposed primarily to nonchlorinated ground water.

Results from toxicologic studies offer a biologic rationale for the associations found here. The THMs chloroform and bromodichloromethane (but neither bromoform nor dibromochloromethane) are carcinogenic in laboratory rodents (*26, 27*), and the brominated THMs are mutagenic in Ames salmonella testing strains (*28*).

More than half the chlorine bound to chlorination by-products is found in the nonvolatile fraction (*5*). Complex mixtures of nonvolatiles, extracted by many methods, are mutagenic in in vitro bacterial testing systems (*29, 32-35*) and transform mammalian fibroblasts in tissue culture (*30, 34*). Several mutagens, including highly active α- and β-chlorinated aldehydes and ketones, have been isolated from finished drinking water or comparable laboratory preparations (*4*).

A feeding study in mice and rats of chloroform-extractable nonvolatile organics from treated surface water reported a significant increase in the incidence of malignant tumors in female mice and in male and female rats, with a dose-response relationship in male and female rats (*40*). Rat tumors included mammary and ovarian adenocarcinomas in females, thyroid tumors in males, and lymphosarcomas in both sexes. In mice, adenocarcinomas (site unspecified), lymphosarcomas, and thyroid tumors were found, primarily in females. Site-specific dose–response information was not available. Various local and systemic tumors were induced, in another investigation, after skin painting rodents with nonvolatile organic concentrates from chlorinated surface waters from several places (*37, 41*).

Chlorinated waters from surface sources are characterized by volatile and nonvolatile chlorination by-products. In this study, risks associated with hot and cold beverage consumption were evaluated independently to distinguish between effects of volatiles and nonvolatiles. If volatiles were implicated, we would expect risk to be associated more with the nonheated than with heated beverages. Results were uneven across the sexes, but effects appeared to be associated with both types of beverages, implying the importance of the nonvolatile component.

Potential effects of the chlorine residual (occurring mostly as hyperchlorous acid at neutral pH) should also be considered. The relatively small number of study subjects who consumed chlorinated ground water, where the chlorine residual could be considered a primary contaminant, precluded our evaluation of exposure to hyperchlorous acid and related compounds in the absence of chlorination by products. There is minimal evidence from animal models. A 10% solution of sodium hypochlorite produced excess skin tumors in 9 of 32 mice that had been given submanifestational doses of 4-nitroquinoline 1-oxide (*38*). However, a sodium hypochlorite solution of lower concentration (1%) did not produce excess tumors when skin-painted on rats previously treated with dimethylbenzanthracene (*39*).

Detection of the relatively small risk differences expected from exposure to carcinogens in the general environment is challenging, and care must be taken in epidemiologic studies to minimize bias and account for risk factors that may confound results. Given the design of this study and its careful execution, it is unlikely that bias from case or control selection influenced our findings (*43*). Bladder cancer risks for cigarette smoking (*58*) and for employment in high-risk occupations (*59*) in this study are consistent with earlier findings (*60*). It is improbable that information on water source and tap water ingestion level was developed differentially for cases and controls because of the indirect linkage to water utility information and lack of knowledge, on the part of both subjects and interviewers, of the hypothesis. There is always the possibility that positive associations observed here were due to an unrecognized bladder cancer risk factor that was associated with both important exposure measures (tap water intake level and chlorinated surface water use). Such a risk factor would have had to induce risks of at least the magnitude we observed.

If undetected bias or effects of an intervening risk factor cannot explain our findings, the proportion of bladder cancer in this study attributable to ingestion of tap water from chlorinated surface sources was 12% (from table 5) (*61*). Among nonsmoking cases, the attributable risk associated with chlorinated surface water use was 27%.

While this investigation goes beyond others in many respects, our findings raise several issues, including distinguishing between the effects of chlorination by-products and other water contaminants as well as further explanation of differences in bladder cancer risk between the sexes and across geographical areas. Beyond these specific issues is a need for confirmation of our overall findings.

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